COR ET VASA 56 (2014) e369–e375

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Original research article – *Special issue: Acute Coronary Syndromes*

Why some patients with acute coronary syndrome hospitalized in a university tertiary centre do not undergo coronary angiography? Results from the AHEAD ACS registry

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ARTICLE INFO

Article history:
Received 30 April 2014
Accepted 28 May 2014
Available online 2 July 2014

Keywords:
Myocardial infarction
Acute heart failure
Coronary angiography
Prognosis

ABSTRACT

Background: To evaluate in-hospital and long-term mortality of patients with acute coronary syndromes (ACS) not having selective coronary angiography (CAG) during hospitalization and to analyze the reasons for conservative approach.

Methods and patients: A single-centre retrospective study using registry data. Over the period from January 2005 to April 2009, a total of 193 ACS patients did not have in-hospital CAG. Fifty-five (28.5%) patients had recent CAG (within the last 12 months) or the procedure was planned after discharge (invasive group "I"). In 138 (71.5%) patients, CAG was not considered at all (conservative approach, group "C"). These subgroups were compared in terms of in-hospital parameters and long-term mortality.

Results: ST-segment elevation myocardial infarction (STEMI) was diagnosed in 50 (25.9%) patients. The most frequent reasons for not performing CAG included serious comorbidities affecting the prognosis (22%) and pharmacological stabilization in very old individuals with non-STEMI (21%). One in ten (11%) patients died before the CAG was performed, the same proportion of patients refused to have CAG or had a long ischaemia time (STEMI subgroup). A temporary contraindication to CAG was found in 8%, a recent CAG finding not suitable for revascularization in 8%, while a limiting neurological disease was present in 6% of patients. In-hospital mortality was 30.1%, being higher in Group C (34.1% vs. 20.0%; $p = 0.049$), 6-year mortality was as high as 78.8%, also with higher rates in Group C (86.2% vs. 60.2%; $p < 0.001$).

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Abbreviations: ACS, acute coronary syndrome; CAG, selective coronary angiography; STEMI ST, segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; AHEADACS, Acute HEArt failure Database – Acute Coronary Syndromes; AHF, acute heart failure; IKK FN Brno, Department of Cardiology and Internal Medicine, University Hospital Brno (Interní kardiologická klinika Fakultní nemocnice Brno); MI, myocardial infarction; UA, unstable angina; BMI, body mass index; LV, left ventricle; ECG, electrocardiography.

http://dx.doi.org/10.1016/j.crvasa.2014.05.005

Patients receiving conservative therapy were older, with a higher proportion of limiting comorbidities that contraindicated CAG, and had a more serious course of hospitalization. *Conclusion:* The most common reasons for not performing CAG in ACS patients included advanced age, serious and often extra-cardiac comorbidities, and a complicated hospitalization course. The short- and long-term mortality rates in these patients are high.

Introduction

Selective coronary angiography (CAG) followed by myocardial revascularization using percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is considered as the optimal procedure in the treatment of acute coronary syndromes (ACS). The superiority of the invasive approach over pharmacological reperfusion with thrombolysis or, alternatively, conservative treatment has been documented both for the population of patients with ST-segment elevation myocardial infarction (STEMI) [1] and non-ST-segment elevation myocardial infarction (NSTEMI) [2]. However, there is a small patient population who do not undergo CAG at all (and treated conservatively), or assessment of their coronary arteries is scheduled later after discharge. The profile of these patients and their long-term prognosis have not been fully characterized yet.

The aim of our study was to characterize patients with the diagnosis of ACS admitted to a cardiology-specialized university tertiary centre who are primarily indicated – despite the immediate availability of angiographic assessment – for conservative treatment, with only pharmacotherapy. The study examines the main reasons of not performing CAG. Within this population, groups of patients with a recent angiogram available (CAG performed within the last 12 months before the admission for ACS) or with planned CAG after discharge (i.e., CAG considered as necessary) are compared with those not primarily indicated for the procedure at all. Both in-hospital and long-term mortality data will also be analyzed.

Methods

Data analyzed in this study were obtained from the AHEAD-ACS (Acute HEArt failure Database – Acute Coronary Syndromes) registry. This multi-centric registry of acute heart failure (AHEAD) was created in 2005 with an effort to investigate the epidemiology, treatment, and prognosis of patients with acute heart failure (AHF) of all aetiologies in Czech Republic, and had a prospective design [3]. Since 2008, the registry has been systematically complemented with data in a retrospective manner to include ACS patients irrespective of the presence of AHF in the largest centre – the Department of Cardiology an Internal Medicine of University Hospital Brno (IKK FN Brno). The purpose of this sub-registry is to evaluate the incidence and effect of AHF in ACS and to establish the long-term prognosis of this patient population (the registry contains long-term mortality data). Data are being collected in a consecutive manner.

The following inclusion criteria were selected for the study: first hospitalization for ACS at IKK FN Brno from 1 January 2005 through 30 June 2008, and hospitalization without performing CAG. The dataset comprises a total of 193 patients. At an average number of 55 patients hospitalized in our centre per month, this number represents about 8% of the total population diagnosed to have ACS. Our study compares the part of this population not indicated for CAG at all (referred to as Group ''C'' hereinafter; $N = 138$) with those patients undergoing CAG recently prior to hospital admission (i.e., performed within the last 12 months but with findings not suitable for revascularization) and/or patients considered for an elective procedure after the discharge, most often with a temporary contraindication for CAG during hospitalization (referred to as group ''I'' hereinafter; $N = 55$).

The parameters compared in the study included data related to the patients' medical history, examinations performed during hospitalization, and treatment (long-term and in-hospital). In addition, the comparison included analysis of total in-hospital and long-term mortality. The follow-up period ranged from 0 to 92 months (with 23 months being the average), and 5 months of median follow-up time. Total mortality data were obtained from the Institute of Health Care Information and Statistics of the Czech Republic (Prague). Patients whose data had been entered into the registry signed their informed consent, the registry protocol was approved by Ethics Committee of the University Hospital Brno, and data collection was made in compliance with the Declaration of Helsinki.

Statistical analysis

Dataset analysis was performed using basic descriptive statistics; because of data asymmetry, median and 5th and 95th percentiles are given for continuous variables, with the proportions of individual categorical variables described by their frequency and percentage counts.

Comparison of patient groups by elective CAG and availability of angiographic finding was performed using the chi-square test for categorical variables, and the Mann–Whitney test for continuous variables. Cumulative mortality curves were assessed using the Kaplan–Meier estimate of survival function, with the individual curves compared using the log rank test. A difference at a level of significance of $\alpha = 0.05$ was considered statistically significant.

The analysis was performed using IBM SPSS Statistics 21 for Windows software (Release 21.0.0, © IBM Corporation 2012)

and R software [R version 2.12.2 (20011-02-25), Copyright © 2011 The R Foundation for Statistical Computing] using a Thomas Lumley (2011) survival package: Survival analysis, including penalized likelihood.

Results

Of the total of 193 patients, CAG was scheduled (after discharge) or their recent CAG finding was available in 55 (28.5%) patients. The mean age of the whole study population was 80 years (range, 52–91), with 77.7% aged over 70 years, and 49.7% aged over 80 years. Patients not indicated for CAG were older [81 (range, 52–93) vs. 76 years (range, 52–86), $p = 0.003$]. Males were present in 54.4% of the whole group ($N = 105$) with a higher proportion in Group I (74.5% vs. 46.4%; $p < 0.001$).

In the whole study population, a baseline diagnosis of STEMI was established in 50 (25.9%) patients, with a higher proportion in Group C (31.2% vs. 14.5%; $p = 0.014$). At discharge, the final diagnosis of Q-wave myocardial infarction (MI) was established in 34.1% of patients, again with a higher proportion in Group C (42.1% vs. 18.6%; $p = 0.014$). Non-Q-MI was diagnosed in 49.3% of patients while 16.7% of patients had unstable angina (UA) with negative cardiac enzymes.

Reasons for conservative approach

Within the whole group of our patients, we identified eight main reasons why physicians chose conservative treatment without performing CAG during hospitalization. These reasons are shown in Fig. 1. The most frequent were serious comorbidities and pharmacological stabilization in very old patients diagnosed to have NSTEMI on admission. One in 10 patients died before CAG could have been performed (mostly immediately after hospital admission, 9.1% of such patients were present in Group I). Among patients receiving primarily conservative treatment a markedly higher proportion of those with prognosis-limiting comorbidities was found (29.7% vs. 3.6% in Group I); there was also a difference in the incidence of patients presenting already in the sub-acute phase of STEMI (15.4% vs. 1.8% in the Group I). Conversely, patients planned for elective CAG, had more often a temporary reason for not undergoing the procedure during the index hospitalization (18.2% infectious disease vs. 2.2% in Group C).

Hospitalization course

Patients considered to undergo CAG had a higher baseline body mass index (BMI) and blood pressure on admission, with suspected ischaemia more often affecting the anterior wall of the left ventricle (LV). On the other hand, patients with conservative approach had a higher incidence of impaired consciousness at admission (Table 1). Patients considered for CAG had more often myocardial revascularization procedures in the past as well as higher long-term use of beta-blockers and lipid-lowering drugs before the hospital admission (Table 2).

A total of 40.6% of patients had echocardiography-documented LV ejection fraction (LVEF) < 40% (moderate LV systolic dysfunction), with a higher average LVEF found in

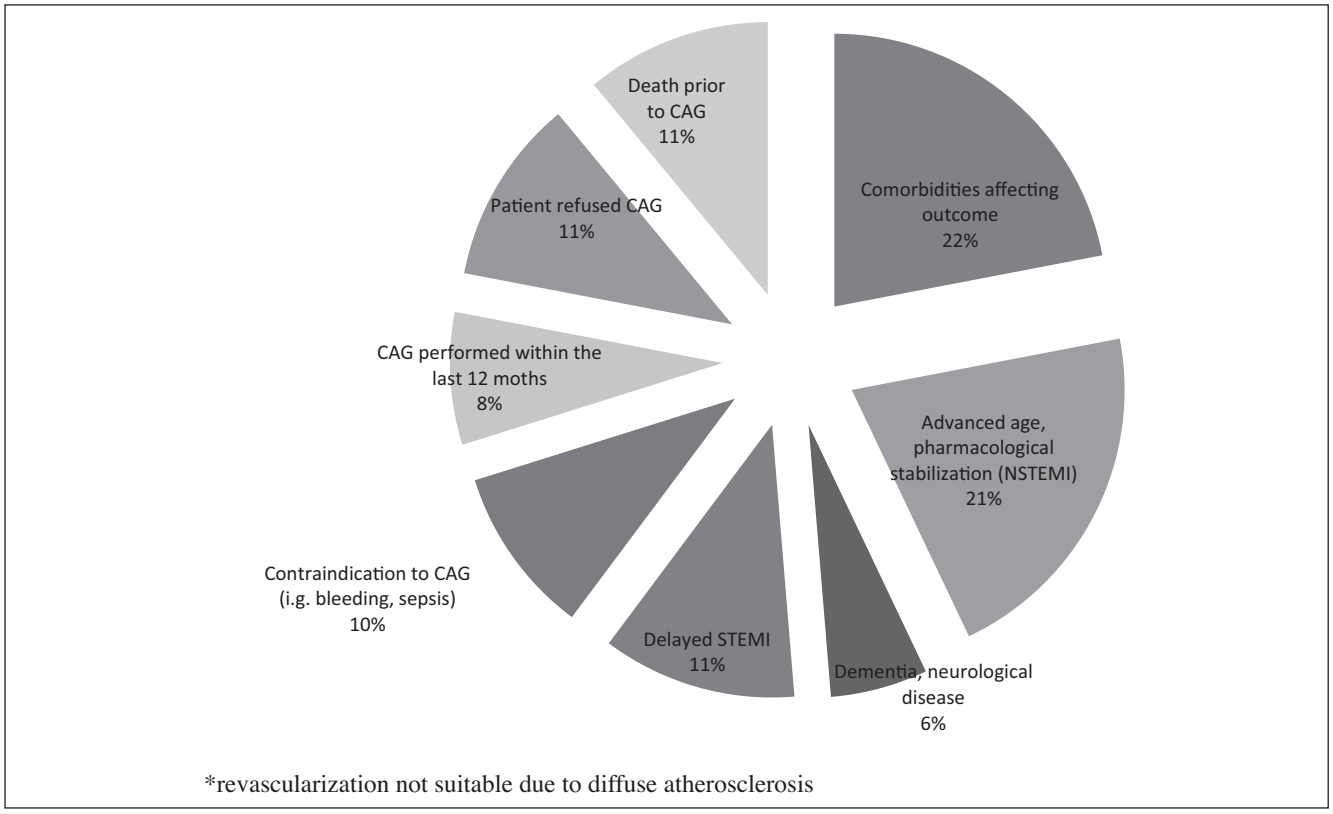


Fig. 1 – Causes of conservative approach in the whole population ($N = 193$).

Table 1 – Clinical assessment at admission and suspected ACS location (ECG, echocardiography).

Parameter	N (%)/median (5th; 95th percentiles)			p
	Total (N = 193)	Group C (N = 138)	Group I (N = 55)	
BMI	26.8(20.8; 38.0)	25.4(20.2; 38.0)	28.4(22.2; 35.4)	**0.044**
Admission systolic BP (mmHg)	140(80; 210)	130(70; 205)	145(90; 230)	**0.004**
Admission systolic BP < 100 mmHg	17.2%	20.4%	9.1%	**0.047**
Admission diastolic BP	75(45; 110)	70(40; 110)	80(50; 130)	0.068
Baseline heart rate (b.p.m.)	93(54; 133)	95(50; 135)	88(55; 120)	0.073
Atrial fibrillation/flutter (ECG)	19.7%	21.7%	14.5%	0.070
QRS ≥ 120 ms (admission ECG)	21.4%	23.8%	15.0%	0.235
Impaired consciousness on admission	14.5%	18.8%	3.6%	**0.003**
Pre-hospital cardiac arrest	2.6%	3.6%	0.0%	0.064
ACS location				
Inferior wall	18.5%	22.4%	9.4%	**0.024**
Lateral wall	6.2%	6.4%	5.7%	
Anterior wall	42.1%	35.2%	58.5%	
Unclear	33.1%	36.0%	26.4%	

BMI, body mass index; BP, blood pressure; ECG, electrocardiography; ACS, acute coronary syndrome. *P*-values below 0.05 are taken as statistically significant.

Table 2 – Personal history and previous chronic treatment.

Parameter	N (%)/median (5th; 95th percentiles)			p
	Total (N = 193)	Group C (N = 138)	Group I (N = 55)	
Hypertension	79.9%	80.7%	77.8%	0.649
Hyperlipidaemia	68.3%	66.3%	73.0%	0.462
Diabetes mellitus	49.7%	52.6%	42.6%	0.214
History of myocardial infarction	43.9%	40.0%	53.7%	0.087
Previous PCI and/or CABG	13.2%	8.9%	24.1%	**0.008**
History of stroke/TIA	23.3%	26.7%	14.8%	0.072
Peripheral arterial disease	12.7%	8.9%	22.2%	**0.017**
Chronic obstructive pulmonary disease	14.3%	14.1%	14.8%	0.896
Smoking	21.7%	20.4%	24.4%	0.289
History of malignancy	11.9%	13.0%	9.0%	0.433
Class III/IV (NYHA) dyspnoea	10.2%	9.0%	13.0%	0.429
Class III/IV (CCS) angina	6.2%	4.3%	10.9%	0.104
Long-term therapy before hospitalization				
Antiplatelet drugs	63.1%	61.1%	67.9%	0.385
RAAS blockers	60.9%	61.1%	60.4%	0.927
Beta-blockers	42.5%	37.3%	54.7%	**0.032**
Lipid-lowering drugs	23.3%	17.4%	38.2%	**0.003**
Oral nitrates	37.4%	34.9%	43.4%	0.287

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischaemic attack; NYHA, New York Heart Association classification; CCS, Canadian Cardiovascular Society classification; RAAS, renin-angiotensin-aldosterone system. *P*-values below 0.05 are taken as statistically significant.

Group I. These patients also less often presented with signs of acute heart failure and or haemodynamic instability (manifested as hypotension requiring vasoactive treatment). Despite similar baseline creatinine levels, conservatively treated patients were more often diagnosed to have acute renal injury during hospitalization (Table 3). This patient population had significantly higher GRACE scores (176 vs. 144 points; $p < 0.001$), with 8 patients experiencing severe in-hospital bleeding (5.8% of Group C).

Mortality

The difference in overall mortality in selected subgroups became evident already during hospitalization. Total in-hospital and 30-day mortality rates were 30.1% and 36.3%, respectively, with significantly poorer outcome in conservatively treated patients [in-hospital mortality of 34.1% vs. 20.0% ($p = 0.049$) and 30-day mortality of 42.8% vs. 20% ($p = 0.002$)]. Long-term mortality rates are shown in Fig. 2. There were up to 86.2% of deaths observed in the population of patients not undergoing CAG over a period of 6 years; on the other hand 6-year mortality in the invasively treated group was 60.2% ($p < 0.001$).

Discussion

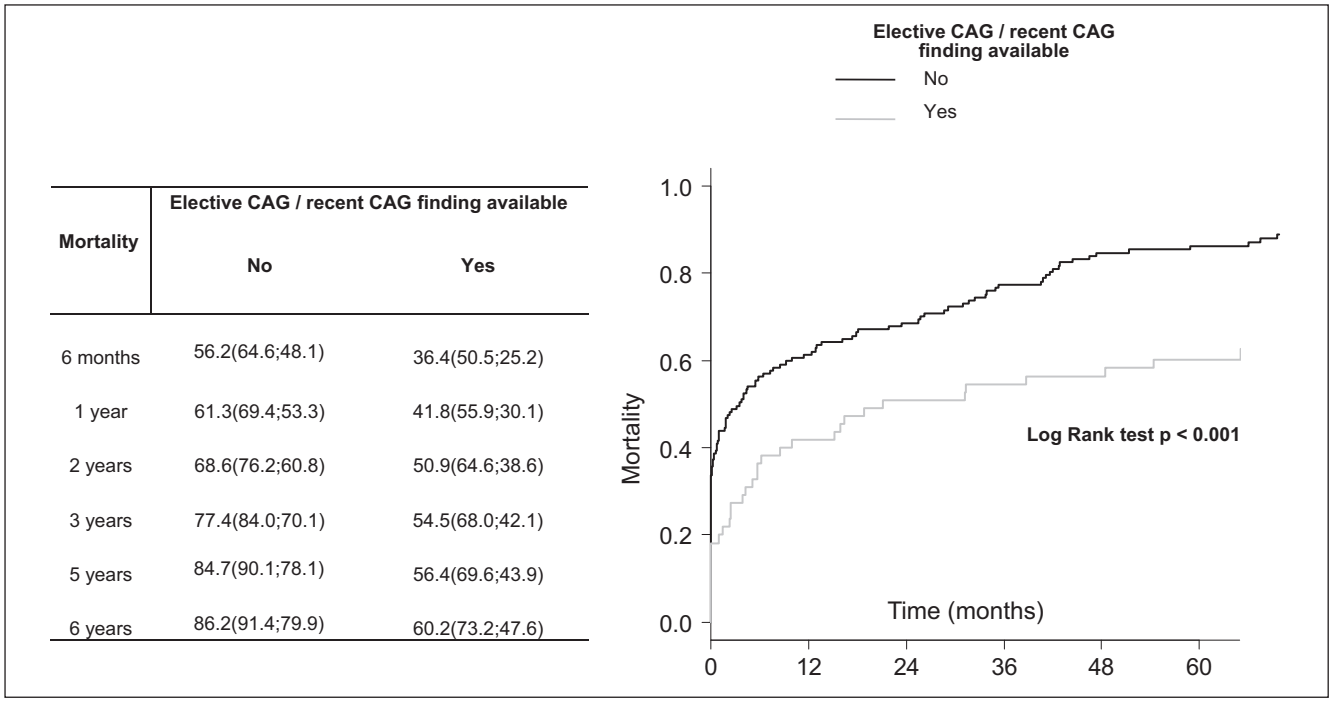
Only less than one tenth of patients admitted for ACS to the tertiary university centre with 24-h PCI service do not have in-hospital CAG, and over two thirds of these patients are not

Table 3 – Hospitalization course.

Parameter	N (%)/median (5th; 95th percentiles)			p
	Total (N = 193)	Group C (N = 138)	Group I (N = 55)	
LVEF (echocardiography)	40.0(20.0; 65.0)	40.0(20.0; 62.0)	47.0(25.0; 65.0)	**0.023**
Signs of acute heart failure	73.6%	78.3%	61.8%	**0.029**
Lung oedema (chest X-ray)	18.1%	21.0%	10.9%	**0.033**
Pleural effusion (chest X-ray)	29.4%	31.7%	22.9%	0.315
Cardiogenic shock	28.0%	32.6%	16.4%	**0.019**
Mechanical pulmonary ventilation	25.9%	29.7%	16.4%	**0.049**
Hypotension requiring treatment	19.2%	9.4%	43.6%	**<0.001**
In-hospital infection/sepsis	48.7%	51.4%	41.8%	0.226
Laboratory assessment				
Baseline haemoglobin (g/L)	127(91; 158)	126(89; 157)	130(99; 159)	0.209
Uric acid (μmol/L)	400(232; 709)	418(202; 800)	344(250; 663)	0.074
Baseline creatinine (μmol/L)	117(71; 266)	117(73; 283)	115(70; 259)	0.989
Maximal creatinine (μmol/L)	130(73; 462)	138(76; 506)	119(70; 393)	**0.028**
Acute kidney injury (AKI)	33.2%	39.1%	18.2%	**0.004**
In-hospital intravenous treatment				
Noradrenaline/adrenaline	31.6%	37.7%	16.4%	**0.003**
Dobutamine/levosimendan	22.3%	27.5%	9.1%	**0.003**
Nitrates	31.6%	29.7%	36.4%	0.373
Diuretics	65.3%	71.7%	49.1%	**0.003**
Antibiotics	49.2%	54.4%	36.5%	**0.030**
Treatment at discharge in surviving patients				
Antiplatelet drugs	92.6%	90.1%	97.7%	0.082
RAAS blockers	80.7%	80.2%	81.8%	0.825
Beta-blockers	81.5%	78.0%	88.6%	0.124
Lipid-lowering drugs	77.8%	73.6%	86.4%	0.085
Oral nitrates	47.4%	41.8%	59.1%	0.058

LVEF, left ventricular ejection fraction; AKI, acute kidney injury – defined as the difference between peak and baseline serum creatinine ≥ 26 (AKI 1) or peak creatinine/baseline creatinine ratio of ≥2 or need for acute haemodialysis (AKI 2). P-values below 0.05 are taken as statistically significant.

indicated for the procedure at all even in the future and receive conservative, pharmacological therapy. Taking account of the well-organized network of PCI and non-PCI hospitals within the Czech Republic, this is a relatively small proportion of patients from a pre-selected group of patients, who are referred from peripheral hospitals to tertiary care centre. The percentage of conservatively managed patients in the primary care hospitals is presumably higher. This is consistent



Mortality	Elective CAG / recent CAG finding available	
	No	Yes
6 months	56.2(64.6;48.1)	36.4(50.5;25.2)
1 year	61.3(69.4;53.3)	41.8(55.9;30.1)
2 years	68.6(76.2;60.8)	50.9(64.6;38.6)
3 years	77.4(84.0;70.1)	54.5(68.0;42.1)
5 years	84.7(90.1;78.1)	56.4(69.6;43.9)
6 years	86.2(91.4;79.9)	60.2(73.2;47.6)

Fig. 2 – Long-term mortality based on the indication for CAG.

with data from the ALERT-CZ registry, where CAG was not undertaken in one out of 10 STEMI patients and in more than one in four patients with the diagnosis of NSTEMI [4]. However, the number of ACS patients undergoing CAG in the Czech Republic is above the European average in general [5,6].

The most frequent reasons why CAG is not performed are serious comorbidities adversely affecting the prognosis and/or multi-morbidity of patients. Almost 50% of patients in our cohort had diabetes mellitus, similarly a history of MI and anaemia documented by laboratory investigations (45.9%), and more than two thirds had renal failure with a creatinine clearance < 60 ml/min (70.5%). About 10% of our patients had a history of cancer. Signs of an infectious disease were detected in 50% of our patients during hospitalization, while a third experienced significant deterioration of renal function.

Current guidelines for myocardial revascularization recommend CAG in all ACS patients. In the subgroup of STEMI patients, the decision to indicate the procedure is based on the assumed ischaemia time [7]. About one half (44.9%) of our STEMI patients did not have CAG because of a long ischaemia time. Another reason was death before the procedure (26.5% of STEMI patients). A tenth of our patients refused to have CAG. It should be emphasized a high mean age (80 years) of our population, which is more frequently associated with atypical symptomatology (absence of angina) as well as relatively poor mobility.

In NSTEMI patients, timing of CAG is dependent on the patient's risk stratification [8]. An initially conservative approach is possible in two subgroups of patients. The first one comprises so called low-risk patients, who are younger, hemodynamically stable individuals without the risk factors of coronary heart disease, with no ECG abnormalities, with negative values of cardiac markers and a early exercise testing without signs of ischaemia. These criteria were met by only five patients of our population. Three patients were planned for CAG at a later time because of acute infection and two patients refused to have the examination. Another subgroup of NSTEMI patients, initially not suitable for an invasive strategy, are patients with excessively high risk associated with invasive procedure or intervention. These are especially individuals with advanced age and serious comorbidities affecting their life expectancy and quality of life that are also increasing the risk of ischaemic and bleeding complications. Advanced age is generally associated with a higher risk of adverse effects of therapeutic interventions. These may especially include bleeding due to antiplatelet and anticoagulation therapy, whose rates could be reduced in the future by the increasing intention to use a radial approach when performing CAG. Another possible complication during invasive procedures in older patients are hypotension, tachycardia as a signs of circulatory failure and contrast-induced acute kidney injury. In our group, signs of renal impairment were seen already at admission in 70.5% of patients, with renal function deteriorating during hospitalization (even without use of contrast agents) in a third.

The overall high risk profile of our study cohort is confirmed by the average GRACE score (168 points). Although an early invasive approach (within 24 h) in patients with a GRACE score > 140 in the TIMACS trial was associated with a 38% reduction of death, MI or stroke at 6 months, there is no doubt that a selective approach is used in clinical practice and that higher age with multiple comorbidities are seen as major limitations of CAG [9]. This is also supported by the fact that, in some studies, patients indicated for CAG paradoxically had GRACE scores lower than those treated conservatively. This inverse relation between the risk profile and the use of invasive approach was also observed in our study [10,11]. The higher mortality rates in patients not indicated for CAG can be associated with overall worse health status of this population whose outcome depends on the presence of another, often extra-cardiac, comorbidities.

Given the advanced age and risk profile of our study population, the relatively high in-hospital and long-term mortality rates are not unexpected. In the study by Terkelsen et al., the in-hospital mortality of patients with a mean age of 80 years and ACS with bundle branch block was 33.3%, with one-year mortality being as high as 54.8% [12]. In another study by Belgian authors, the in-hospital mortality rate in STEMI patients aged over 80 years was 17.8%; however, in patients with signs of heart failure, it was markedly high regardless of the therapeutic strategy (PCI subgroup 34.6%, patients treated with thrombolysis 31.6%, conservative approach 36.3%; $p = 0.88$) [13].

Limitations

The study was conducted in a single university centre specialized in cardiology admitting only a small proportion of unselected internal medicine patients, thus does not exactly reflects the epidemiological status of ACS patients receiving conservative treatment. A more accurate estimate of the numbers of these patients could be obtained in departments of internal medicine of regional hospitals with exclusively unselected hospital admissions. However, the study identifies reasons of conservative approach without performing CAG despite its immediate availability. Because of the retrospective nature of the data capture, we cannot exclude, that some of the patients could undergo CAG in the future. Furthermore, the study documented a relatively high proportion of patients experiencing in-hospital acute heart failure. As the data were extracted predominantly from an acute heart failure registry, we cannot rule out that, in some cases, the diagnosis may have been established mainly on the basis of elevated cardiac enzymes associated with acute heart failure per se. This fact may have resulted in an overlap of the diagnoses.

Conclusion

Only a small proportion of patients admitted to a specialized cardiac university centre for ACS do not undergo invasive examination of coronary arteries despite its immediate availability. Over two thirds of these patients are not indicated for coronary angiography even in the future and after the elimination of relative contraindication for the procedure (e.g., bleeding or infective disease). This population is characterized by advanced age, multiple comorbidities, and a complicated hospitalization course and probably will not benefit from an invasive approach. Their outcome is frequently related to another, often extra-cardiac disease. The short- and long-term mortality rates of these patients are high.

Conflict of interest

The authors declare they have all participated in developing the manuscript and have approved its final version for publication. The authors also declare they have no financial or other commitments that could possibly result in a conflict of interest.

Funding body

Supported by the European Regional Development Fund, project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123).

Ethical statement

All the work was conducted in accordance with the Declaration of Helsinki. Local ethics committees of involved centres approved the study protocol.

Informed consent

An informed consent was obtained from all the participants in the study prior to their inclusion.

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